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(54) Topical drug delivery systems containing danazol.

(57) A topical drug delivery system comprises as a matrix base, danazol retained therein, and optionally a release-promoting agent. Such a system is more effective than oral administration of danazol in the shrinkage of endometriosis tissue, and the induction of pregnancy. It does not show any side effects that have been encountered in the oral administration of danazol.

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Topical Drug Delivery Systems Containing Danazol

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to danazol-containing topical drug delivery systems which are markedly effective in the treatment of pelvic endometriosis and uterine adenomyosis. More particularly, it relates to intrauterine and vaginal devices comprising a matrix base having danazol retained therein.

Endometriosis is a disease which occurs mostly in mature women and is frequently associated with infertility. According to the site of the focus, it is broadly divided into pelvic endometriosis (external endometriosis) and uterine adenomyosis (internal endometriosis).

Danazol is a drug which is well thought of and widely used as an oral remedy for endometriosis ("Gekkan Yakuji", Vol. 25, No. 4, p. 691, 1983), but its effectiveness as a topical remedy has never been discussed or shown. This seems to be due to the fact that two theories are widely supported in connection with the mode of action of orally administered danazol. One of them is the theory that orally administered danazol suppresses the function of the hypothalamohypophyseal system to decrease the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which results in decreased secretion of estrogens by the ovary and the eventual shrinkage of endometriosis tissue (Fertility and Sterility, Vol. 29, p. 637, 1978). In other words, this theory insists that oral administration of danazol provides a pseudomenopausal therapy which completely suppresses the function of the ovary. The other theory is a modified version of the foregoing theory, but claims an appreciable direct effect on endometriosis cells (American Journal of Obstetrics and Gynecology, Vol. 140, p. 62, 1981).

Meanwhile, almost all women suffering from endometriosis become infertile. As pelvic endometriosis develops, menstrual pain appears and further aggravation results in a complaint of non-menstrual pain in the loins or lower abdomen. In cases of uterine adenomyosis, many patients complain of menstrual pain and hypermenorrhea in addition to infertility. Thus, most patients with endometriosis consult a doctor for medical advice about their infertility. It is only a few that complain chiefly of menstrual pain and have no desire for pregnancy in the future. In other words, the desire of most patients is the success of pregnancy, and

a secondary desire.

However, oral administration of danazol is ineffective in most cases of uterine adenomyosis. On the other hand, orally administered danazol is highly effective in treating pelvic endometriosis, but has the following disadvantages. (1) The patient is utterly unable to conceive during and soon after the treatment because ovulation is suppressed. (2) The pregnancy rate after discontinuance of the treatment is low. (3) It is not uncommon for endometriosis to reoccur several months after discontinuance of the treatment.

As a result of intensive investigations, I have now unexpectedly found that (1) intrauterine application of danazol has a marked effect on uterine adenomyosis for which oral administration has been virtually ineffective; (2) vaginal application of danazol does not suppress ovulation even during treatment and the patient may become pregnant even during treatment; (3) a high pregnancy rate is achieved as contrasted with oral administration; (4) prolonged vaginal application of danazol can prevent the recurrence of endometriosis which is often encountered after discontinuance of its oral administration; and (5) topical application of danazol is not associated with such side effects as are often encountered in its oral administration, such as weight gain aggravation of acne, transient hepatic functional disorder and the like. Thus, I believe I have demonstrated an error in conventional thinking that the effect of danazol on endometriosis is produced solely by suppressing the endocrine functions of the hypothalamus-hypophysis-ovary system.

SUMMARY OF THE INVENTION

The present invention has first clarified, from a clinical point of view that danazol has a direct effect on endometriosis cells, that this direct effect is much more important than the suppressive effect on the hypothalamus-hypophysis-ovary system, and that it has also demonstrated the lack of understanding in the foregoing established and corrected theories in which pseudomenopausal therapy is considered to be the basis of danazol treatment. The present invention, it is believed, involves the first instance of topical application of danazol.

According to the present invention, there is provided a topical drug delivery system comprising a matrix base, danazol retained therein, and optionally a release-promoting agent, in a form suitable

The shape of the delivery system may be any of the various shapes commonly employed for insertion into and retention within a uterus or vagina. Typically, they can be shaped like the letter T or Ota's ring when they are designed for insertion into the uterus, and can be shaped like an annulus when they are designed for insertion into the vagina.

The size of the device should desirably be as follows: For T-shaped intrauterine device, the horizontal member may have a length of 20 to 40 mm, preferably 30 to 35 mm, and a diameter of 1.0 to 3.0 mm, preferably 1.8 to 2.6 mm, and the vertical member may have a length of 25 to 45 mm, preferably 30 to 38 mm, and a diameter of 3.0 to 4.0 mm, preferably 3.2 to 3.6 mm. For Ota's ring-like intrauterine device, they may have an outer diameter of 20 to 25 mm and a ring thickness of 2.5 to 4.5 mm, preferably about 3.0 mm. For annular vaginal devices they may have an outer diameter of 30 to 60 mm, preferably 45 to 55 mm, and a ring thickness of 4.0 to 12.0 mm, preferably 7.5 to 10.0 mm.

T-shaped or Ota's ring-like intrauterine devices will usually have a single-layer structure. However, in order to enhance their rigidity, they may have a two-layer structure in which a core comprising a piece of Silascon Rod (manufactured by Dow Corning Co.) or other material is embedded. Where a core is embedded in T-shaped intrauterine devices, a satisfactory result can usually be obtained by embedding the core only in the horizontal member. Preferably, the length of the core should be in the range of 55 to 70 % of the length of the horizontal member used, and the diameter of the core should be in the range of 60 to 90 % of the diameter of the horizontal member. In the case of T-shaped intrauterine devices, it is necessary to attach cord, such as a nylon monofilament, to the lower end of the vertical member. A nylon monofilament should have a length of 30 to 400 mm, preferably 50 to 280 mm, and a diameter of 0.270 to 0.290 mm. On the other hand, annular vaginal devices may be configured so as to have a single-layer or a two-layer structure, with a view to controlling the degree of release of the active component according to the duration of treatment and the severity of symptoms. However, where annular vaginal devices have a two-layer structure, the outer layer should have a thickness of at least 0.1 mm and preferably 0.1 to 2.0 mm.

The content of the active component, i.e., danazol, in drug delivery systems of the present invention may be in the dosage range where, during topical application, the beneficial effects of danazol can manifest themselves according to the duration of treatment and the severity of symptoms. Ideally, the content of danazol should be in

the range of 80 to 200 mg, preferably 100 to 180 mg, for intrauterine devices and in the range of 50 to 4000 mg, preferably 90 to 3500 mg, for vaginal devices. Where the content of danazol in vaginal devices is selected to be as low as 1000 mg or less, it is desirable that they have a two-layer structure in which the outer layer has the selected content of danazol.

Preferably, the drug delivery systems should be made so as to have a composition comprising 20 to 50 parts by weight of the active component, i.e., danazol, 50 to 80 parts by weight of the matrix base, and optionally 0.5 to 8 parts by weight of the release-promoting agent. When providing a two layer structure the outer layer should contain the danazol. The core may be formed as defined above or comprise any suitable material formed into any desired shape and size. The material used for this purpose may be of the same type as or a different type from the matrix base.

As described above, the drug delivery systems contain danazol and a matrix base as essential components and a release-promoting agent as an optional component. In addition to these components, they may contain a very small amount of a vulcanization catalyst on the basis of their manufacturing method.

The matrix base used in the delivery system may be selected from various polymeric compounds which are widely used in intrauterine or vaginal drug delivery systems and authorized for medical use. Specific examples thereof include silicone rubber (polydimethylsiloxane), silicone-carbonate copolymer, ethylene-vinylacetate copolymer, ethylene-vinylalcohol copolymer, polyethylene, polymethyl methacrylate, polyhydroxyethyl methacrylate, polyisobutylene, polycarbonate, polybutylmethacrylate, natural gum, polyalkylcyanoacrylate, ethylcellulose, carboxymethylethylcellulose, polyethylene glycol, polyvinyl alcohol, carboxyvinyl polymer and collagen. However, polydimethylsiloxane, silicone-carbonate copolymer, ethylene-vinylacetate copolymer and ethylene-vinylalcohol copolymer are most preferred from the viewpoint of the retention and release of danazol. The term "matrix base" as used herein comprehends various types of matrix base which may contain a cross-linking agent according to need. The cross-linking agent may be any of those commonly used in various drug delivery systems, according to the type of the matrix base. Commercial products of polydimethylsiloxane can be used for the aforesaid purpose, and typical examples thereof are MDX-4-4210 (containing a cross-linking agent) and Silastic 382 (both manufactured by Dow Corning Co.). The release-promoting agent which is used as an optional component may be selected from Polysorbate 60, Polysorbate 80, glycerol,

isopropyl palmitate, isopropyl myristate and the like.

The drug delivery systems can be made according to standard techniques for the manufacture of intrauterine or vaginal preparations and devices. For example, single-layer devices are made by charging danazol, a matrix base and, if desired, a release-promoting agent into a vessel, adding a vulcanization catalyst thereto, mixing these ingredients at room temperature for 2 to 30 minutes, pouring the resulting mixture into a mold, and solidifying it at room temperature. The contents or weight ratios of danazol, the matrix base and the release-promoting agent may readily be selected so as to fall within the aforesaid ranges and the mold should be one which gives the above-described shape and size. The vulcanization catalyst may comprise a tin catalyst or a platinum catalyst and should be used in an amount of 0.1 to 2.0 % by weight, preferably 0.5 to 1 % by weight, based on the amount of the matrix base. Two-layer devices are made according to substantially the same procedure as described above for single-layer preparations, but include the additional step of embedding a desired core into the mixture, after pouring it into the mold. The core may comprise any of the above-described materials. Since the present preparations must be sterile products on the basis of their usage, they should be made under sterile conditions. It is to be understood that the final products are packaged in a conventional manner, e.g. with heat-sealable aluminium packaging material.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The rate of release of danazol from drug delivery systems of the present invention will be described hereinbelow. The rate of release was tested in two different ways, i.e., by in vitro tests and by clinical tests.

In vitro tests

A number of delivery systems made in accordance with the present invention were each suspended in 2 to 3 liters of distilled water and held at 37°C for 8 to 44 days with stirring of the water. The amount of danazol released into the water per day was determined by liquid gas chromatography. During the test period, the distilled water was replaced every day.

The amount of danazol released per day was about 250 to 400 µg for intrauterine preparations

and about 1000 to 3000 µg for vaginal preparations.

Clinical tests

A number of devices made in accordance with the present invention were each inserted into the uterus or vagina of 50 patients with endometriosis, aged 28 to 39, and retained therein for 2 to 30 weeks. The amount of release of danazol per day was determined by calculating the difference between the danazol contents of the device at the beginning and the end of the insertion, and dividing it by the number of days of insertion. The danazol content of each device was determined by extracting the device with chloroform and measuring the amount of danazol present in the extract by absorption photometry.

The amount of danazol released per day was about 150 to 300 µg for intrauterine devices and about 900 to 3000 µg for vaginal devices.

Example 1 (vaginal devices)

I) A vessel was charged with 20 g of danazol, 75 g of Silastic 382 and 5 g of Polysorbate 80. After the addition of 1.2 g of a tin catalyst, these ingredients were mixed at room temperature for 20 minutes. The resulting mixture was poured into three types of molds and solidified by allowing the molds to stand at room temperature for one day. Thus, there were obtained a total of 6 single-layer annular vaginal devices as described below, two for each type.

(1) Danazol content: 2300 mg.

Size: 55 mm in outer diameter, 9.5 mm in ring thickness.

(2) Danazol content: 2200 mg.

Size: 52.5 mm in outer diameter, 9.5 mm in ring thickness.

(3) Danazol content 2100 mg.

Size: 50 mm in outer diameter, 9.5 mm in ring thickness.

II) The same procedure as described in paragraph I) above was repeated, except that the amount of danazol was increased from 20 g to 30 g, the amount of Silastic 382 was decreased from 75 g to 70 g, and the addition of Polysorbate 80 was omitted. Thus, there were obtained a total of 6 single-layer annular vaginal devices as described below, two for each type.

(1) Danazol content: 3500 mg.

Size: 55 mm in outer diameter, 9.5 mm in ring thickness.

(2) Danazol content: 3300 mg.
Size: 52.5 mm in outer diameter, 9.5 mm in ring thickness.

(3) Danazol content: 3200 mg.
Size: 50 mm in outer diameter, 9.5 mm in ring thickness.

Example 2 (vaginal devices)

Using a mixture composed of 55 g of MDX-4-4210 (containing a cross-linking agent) and 0.5 g of a platinum catalyst, core rings having an outer diameter of 48.5 mm and a thickness of 5.5 mm were prepared in advance.

Thus, 15 g of danazol, 38.5 g of MDX-4-4210 (containing a cross-linking agent) and 0.35 g of a platinum catalyst were mixed at room temperature for 30 minutes. The resulting mixture was poured into molds and the previously prepared core rings were embedded therein. The mixture solidified by allowing the molds to stand at room temperature for one day. Thus, there were obtained 6 two-layer annular vaginal devices as described below. These devices had an outer layer of 2.0 mm thickness.

Danazol content: 2200 mg.
Size: 52.5 mm in outer diameter, 9.5 mm in ring thickness.

Example 3 (intrauterine devices)

I) 3.00 g of danazol, 11.25 g of Silastic 382 and 0.5 g of Polysorbate 80 were mixed. After the addition of 0.18 g of a tin catalyst, the mixing was continued for 15 minutes. The resulting mixture was poured into T-shaped molds and allowed to solidify by allowing the molds to stand at room temperature for one day. Thus, there were obtained 20 single-layer T-shaped intrauterine devices as described below. A nylon monofilament was attached when the mixture was poured into each mold.

Danazol content: 116 mg.
Size: Horizontal member; 32 mm in length, 2.6 mm in diameter.
Vertical member ; 36 mm in length, 3.6 mm in diameter.
66-nylon monofilament: 54 mm in length, 0.285 mm in diameter.

II) The same procedure as described in paragraph I) above was repeated, except that the amount of danazol was increased from 3.00 g to 4.5 g, the amount of Silastic 382 was decreased from 11.25 g to 10.5 g, and the addition of Polysorbate 80 was omitted. Thus, there were obtained 20 single-layer T-shaped intrauterine devices as de-

scribed below.

Danazol content: 175 mg.

Size: Horizontal member; 32 mm in length, 2.6 mm in diameter.

5 Vertical member ; 32 mm in length, 3.6 mm in diameter.

Yellow nylon monofilament: 280 mm in length, 0.277 mm in diameter.

10 III) The same procedure as described in paragraph II) above was repeated, except that a core comprising a piece of Silascon Rod having a length of 20 mm and a diameter of 1.6 mm was embedded in the mixture poured into each mold. Thus, there were obtained 20 two-layer T-shaped intrauterine devices as described below.

15 Danazol content: 108 mg.

Size: Horizontal member; 32 mm in length, 1.8 mm in diameter.

20 Vertical member; 32 mm in length, 3.2 mm in diameter.

Yellow nylon monofilament: 250 mm in length, 0.277 mm in diameter.

25 Example 4 (intrauterine devices)

1.5 g of danazol, 3.5 g of Silastic 382 and an appropriate amount of a tin catalyst were mixed at room temperature for 10 minutes. The resulting mixture was poured into molds in which a core ring comprising a ring of Silascon Rod having an outer diameter of 20.5 mm and a thickness of 1.6 mm was placed. The mixture was solidified by allowing the molds to stand for one day. Thus, there were obtained 10 two-layer Ota's ring-like intrauterine devices as described below.

35 Danazol content: 90 mg.

Size: 22 mm in outer diameter, 3.0 mm in ring thickness.

40 The effects of the devices described above on endometriosis will now be described. The description will be separately given with respect to Pelvic endometriosis (external endometriosis) and cases of adenomyosis (internal endometriosis) will be described separately.

45 Pelvic endometriosis

50 In 46 patients, aged 28-37, who had been diagnosed as cases of pelvic endometriosis, a vaginal device made in the same manner described in Example 1 was inserted into the vagina for purposes of treatment. These 46 cases included 32 cases in which oral administration of danazol had been found to be ineffective. The period of treatment was up to 30 weeks and the site of insertion of the device was around the opening of the uterus.

(1) Effect on endometriosis tissue in the uterine cul-de-sac

In all of the 46 cases, a marked decrease of endometriosis tissue in the uterine cul-de-sac was noted. Specifically, in 12 cases in which the size (or area) of the tissue was 10-12 cm² at the start of the treatment, it was reduced to 2-3 cm² in the 2nd week. Similarly, 31 cases showed a reduction from 6-8 cm² to 0.5-3 cm² in the 4th to 8th week, and 1 case showed a reduction from 3 cm² to 1 cm² in the 4th week. In the 12th to 17th weeks, the size of the tissue was reduced to 0-0.5 cm² in all of these 44 cases. In the other 2 cases (in which the size of the tissue was 8 cm² or 6 cm² at the start of the treatment), the size of endometriosis tissue in the cul-de-sac was not reduced to 0.5 cm² or less by the 12th to 17th week. The reason why no improvement was observed in these cases seems to be that, since they had adhesive retroflexion of the uterus due to endometriosis in the cul-de-sac and the treatment brought about shrinkage and softening of the endometriosis tissue, the fundus of the uterus could be directly touched by bimanual examination, resulting in an increased volume of palpable tissue. The degree of effectiveness was 100 %.

(2) Effect on tenderness in the uterine cul-de-sac

An improvement of tenderness in the cul-de-sac was noted in all of the 46 cases. A complete cure was achieved in 33 cases, and the average time required for the complete cure was 17.2 weeks. In the other 13 cases, the tenderness was not completely cured, but ameliorated. In one case observed for 17 weeks, pregnancy resulted from homologous artificial insemination (AIH). The degree of effectiveness was 100 %.

(3) Effect on menstrual pain

Menstrual pain was completely cured in 32 out of the 46 cases and ameliorated in 11 cases. The average time required for the amelioration of pain was 5.3 weeks and the average time required for the complete disappearance of pain was 14.3 weeks. The degree of effectiveness was 93.5 %.

(4) Effect on non-menstrual pain in the lower abdomen or loins

Of the 46 cases, 20 complained of non-menstrual pain in the lower abdomen or loins at the start of the treatment. In all of these cases, the pain

disappeared in an average of 6.7 weeks. The other 26 cases did not complain of such pain at the start of the treatment. The degree of effectiveness was 100 %.

(5) Induction of pregnancy

Of the 46 cases, 11 became pregnant during insertion of the vaginal device of the present invention. The pregnancy resulted from sexual intercourse in 10 cases and from homologous artificial insemination in the other one. It is quite surprising that, in contrast to oral administration of danazol during which the patient never becomes pregnant, the vaginal device of the present invention allowed the patient to become pregnant even during treatment. In consideration of the above-described results and the fact that these patients had failed to conceive for the past several years, it is evident that (1) the patients being treated with the devices according to the present invention are not only able to conceive, but more likely to conceive than before treatment and (2) even during treatment, ovulation is not suppressed and spermatozoa are not prevented from passing through the cervical mucus. The degree of effectiveness was 24 %. Just after confirming the establishment of pregnancy, the vaginal ring was removed. They all delivered normal babies with no congenital abnormality.

(6) Other effects

In all of the 46 cases, neither suppression of ovulation nor decrease in blood FSH or LH was noted during treatment. Moreover, the devices did not show such side effects as are encountered in the oral administration of danazol, including a weight gain, an aggravation of acne, an increase of GOT and GPT, and the like.

Uterine adenomyosis

In 4 patients, aged 34-39, who had been diagnosed as cases of uterine adenomyosis, an intra-uterine device made in the same manner described in Example 3 was inserted into the uterus for purposes of treatment. These 4 cases included one case in which oral administration of danazol had been found to be ineffective. The period of treatment was up to 4 months and the site of insertion of the device was within the uterus.

(1) Effect on the corpus of the uterus

In all of the 4 cases, a marked reduction in size of the corpus of the uterus was noted. The length of time required for the onset of shrinkage of the corpus of the uterus was within 2 weeks in all cases. The degree of effectiveness was 100 %.

(2) Effect on menstrual pain

In all of the 4 cases, an amelioration of menstrual pain was noted in an average of 7 weeks after the start of the treatment. Of these case, 3 were completely cured (i.e., the pain disappeared completely) in an average of 14.6 weeks. The degree of effectiveness was 100 %.

(3) Effect on non-menstrual pain in the lower abdomen or loins.

At the start of the treatment, 3 out of the 4 cases complained of non-menstrual pain in the lower abdomen or loins. In all of these 3 cases, the pain disappeared in an average of 6.6 weeks. The degree of effectiveness was 100 %.

(4) Induction of pregnancy

Of the 4 cases, 2 became pregnant immediately after removal of the intrauterine device. The degree of effectiveness was 50 %.

As described above, the devices are more effective than oral administration of danazol in the shrinkage of endometriosis tissue, the induction of pregnancy, and the like. Moreover, they do not show any side effects that have been encountered in the oral administration of danazol. Accordingly, it may safely be said that the devices have provided a novel and very useful remedy for endometriosis.

Claims

1. A drug delivery system comprising a matrix base, danazol retained therein, and optionally a release-promoting agent, in a form suitable for topical administration.

2. A drug delivery system as claimed in claim 1 in a form suitable for insertion into and retention within a uterus.

3. A drug delivery system as claimed in claim 1 or claim 2 which has a danazol content of 80 to 200 mg and which comprises 20 to 50 parts by weight of danazol, 50 to 80 parts by weight of the matrix base, and optionally 0.5 to 8 parts by weight of a release-promoting agent.

4. A drug delivery system as claimed in any one of the claims 1 to 3 wherein the matrix base is selected from polydimethylsiloxane, silicone-carbonate copolymer, ethylene-vinylacetate copolymer and ethylene-vinylalcohol copolymer.

5. A drug delivery system as claimed in any one of the claims 1 to 4 which has the shape of the letter T and which comprises a horizontal member having a length of 20 to 40 mm and a diameter of 0.1 to 3.0 mm, and a vertical member having a length of 25 to 45 mm and a diameter of 3.0 to 4.0 mm.

6. A drug delivery system as claimed in any one of claims 1 to 4 which is substantially Ota's ring-shaped and which has an outer diameter of 20 to 25 mm and a ring thickness of 2.5 to 4.5 mm.

7. A drug delivery system as claimed in claim 1 in a form suitable for insertion into and retention within a vagina.

8. A drug delivery system as claimed in claim 1 or claim 7 which has a danazol content of 50 to 4000 mg and which comprises 20 to 50 parts by weight of danazol, 50 to 80 parts by weight of the matrix base, and optionally 0.5 to 8 parts by weight of the release-promoting agent.

9. A drug delivery system as claimed in claim 7 or claim 8 wherein the matrix base is selected from polydimethylsiloxane, silicone-carbonate copolymer, ethylene-vinylacetate copolymer and ethylene-vinylalcohol copolymer.

10. A drug delivery system as claimed in any of claim 7 to 9 which has the the shape of an annulus and which has an outer diameter of 30 to 60 mm and an annulus thickness of 4.0 to 12.0 mm.

11. A drug delivery system as claimed in any one of claims 1 to 10 which has a single-layer structure or a two-layer structure including a core.

12. Use of a drug delivery system as claimed in any one of the preceding claims, in the treatment of pelvic endometriosis and/or uterine adenomyosis.

13. Use of danazol in the preparation of a medicament for intrauterine or intravaginal administration in the treatment of pelvic endometriosis and/or uterine adenomyosis.



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which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 88312441.4
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	US - A - 4 115 563 (P.M.JOHN) * Claims 1,2,4,5; column 1, lines 10-13; column 3, lines 10-17 *	1,3,8	A 61 K 31/58 A 61 K 9/00 //C 07 J 71/00
A	B.HELWIG, M.HELWIG "Moderne Arzneimittel" fifth edition, 1980 WISSENSCHAFTLICHE VERLAGSGESELLSCHAFT M.B.H, Stuttgart page 1302 * Winobanin R *	1,13	
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			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
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INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: 1-11,13 Claims searched incompletely: 12 Claims not searched: Reason for the limitation of the search: Method for treatment of the human or animal body by therapy EPC article 52(4)</p>			
Place of search VIENNA		Date of completion of the search 05-06-1989	Examiner MAZZUCCO
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
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A	US - A - 4 012 497 (G.SCHÖPFLIN) * Claims 1,4,6-9 *	1,2,4, 7,9-11	